Transgenerational effects of ERalpha36 over-expression on mammary gland development and molecular phenotype: clinical perspective for breast cancer risk and therapy.

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Growing source of evidence suggests that exposure to estrogen mimicking agents is a risk factor for breast cancer onset and progression. Long chain alkylphenols are man-made compounds still present in household products, industrial and agricultural processes, leading to a global environmental and human contamination. These molecules are known to exert estrogen-like activities through binding to classical estrogen receptors. Recently, we have demonstrated that a realistic mixture of 4-tert-octylphenol and 4-nonylphenol can stimulate proliferation and modulate epigenetic status of testicular cancer germ cells through a rapid, Estrogen Receptor alpha 36 (ERα36)- dependent non genomic pathway (Ajj et al, 2013; doi: 10.1371/journal.pone.0061758). In a retrospective study of breast tumor samples, we also validated ERα36 expression as a reliable prognostic factor for cancer progression from an estrogen dependent proliferative tumor toward an estrogen dispensable metastatic disease (Chamard-Jovenin et al, 2015; doi: 10.1186/s12918-015-0178-7).
Since high ERα36 expression enhances expression of migration/invasion markers in breast tumors, we addressed the question of its involvement in response to alkylphenol exposure in vitro (MCF-10A mammary epithelial cell line and MCF-7 estrogen-sensitive cancer cells) and in vivo (C57BL mice).
A male inherited transgenerational model of exposure to environmentally relevant doses of an alkylphenol mix was set up in C57BL/6J mice to determine whether and how it impacts on mammary gland morphogenesis. Human mammary epithelial MCF-10A cells were exposed to similar doses to decipher the molecular mechanisms involved by a combination of transcriptomic study, cell phenotype analyses, functional and signaling network modeling. The relevance of mouse phenotype extrapolation to human risk is discussed.
Mouse mammary gland exposed transgenerationally to the alkylphenol mix displayed a neoplastic-like histology. This phenotype was correlated with the enhanced proliferation, migration ability and apoptosis resistance observed *in vitro* on human mammary epithelial cells and mediated by the estrogen receptor variant ERα36.
Since cellular phenotypes are similar *in vivo* and *in vitro* and involve the unique ERα36 human variant, such consequences of alkylphenol exposure could be extrapolated from mouse model to human. Low dose alkylphenol transgenerational exposure could promote abnormal mammary gland development and subsequently increase the risk of breast cancer at ageing.

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